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Cortisol Levels in Relation to Maternal Interaction and Child Internalizing Behavior in Preterm and Full-Term Children at 18 Months Corrected Age

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Abstract

Cortisol levels were compared in children born preterm at extremely low gestational age (ELGA; 24–28 weeks), very low gestational age (VLGA; 29–32 weeks), and full-term in response to cognitive assessment at 18 months corrected age (CA). Further, we investigated the relationship between maternal interactive behaviors and child internalizing behaviors (rated by the mother) in relation to child cortisol levels. ELGA children had higher “pretest” cortisol levels and a different pattern of cortisol response to cognitive assessment compared to VLGA and full-terms. Higher cortisol levels in ELGA, but not full-term, children were associated with less optimal mother interactive behavior. Moreover, the pattern of cortisol change was related to internalizing behaviors among ELGA, and to a lesser degree VLGA children. In conclusion, our findings suggest altered programming of the hypothalamic-pituitary-adrenal (HPA) axis in preterm children, as well as their greater sensitivity to environmental context such as maternal interactive behavior.

Keywords

cortisol; preterm; stress; anxiety; HPA axis; internalizing behavior; toddler; maternal care; low birth weight; maternal interaction

INTRODUCTION

Stress during early development can permanently reorganize neurobiological, hormonal and physiological systems (Heim & Nemeroff, 2002). Children born preterm are especially at risk based on the immaturity of the cortical cytoarchitecture (Miller et al., 2006; Volpe, 2001) as well as neurotransmitter and neuroendocrine systems (Herlenius & Lagercrantz, 2004; Retz, Kornhuber, & Riederer, 1996). During the neonatal period, when infants born very preterm may be in the neonatal intensive care unit (NICU) for many weeks, cortisol

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levels are often inappropriately low considering the stress of illness (Fernandez, Montman, & Watterberg, 2008; Hanna et al., 1993; Kari, Raivio, Stenman, & Voutilainen, 1996) and repeated skin-breaking procedures (Grunau et al., 2005). Consistent with early "programming" of the hypothalamic-pituitary-adrenal (HPA) axis (Matthews, 2002; Meaney, Szyf, & Seckl, 2007), an adverse neonatal environment, in the context of an immature neuroendocrine system, may induce permanent changes in HPA activity and regulation.

In a larger heterogeneous sample of infants in the same cohort, we have previously reported that pretest cortisol levels of infants born at extremely low gestational age (ELGA; ≤28 weeks gestation) and very low gestational age (VLGA; 29–32 weeks gestation) were significantly below those of full-term infants at 3 months corrected age (CA; age adjusted for prematurity) (Grunau et al., 2007). Importantly, there was a switch at 8 months CA with ELGA infants showing higher cortisol levels than VLGA and full-terms—a pattern that persisted to 18 months CA (Grunau et al., 2007). At age 8–14 years, Buske-Kirschbaum et al. (2007) reported higher early morning cortisol levels in children born preterm. Together, these findings suggest altered programming of the HPA axis in preterm children. Given the importance of cortisol in the regulation of behavior and cognition, and the vulnerability of this population to problems in neurodevelopment (Grunau, Holsti, & Peters, 2006), it appears crucial to understand the etiology of these differences, as well as contextual influences that may modulate development of the HPA axis in children born very preterm.

It is well established that parental care plays an important role in offspring stress regulation and development. Animal studies have shown that maternal care can impact offspring's neuroanatomy and phenotype (Champagne & Curley, 2009; Champagne & Meaney, 2001; Weaver et al., 2004). For example in rats, offspring of dams that spend less time licking and grooming their pups showed increased responses to acute stress and decreased levels of glucocorticoid receptors compared to offspring from "high licking-grooming" dams (Liu et al., 1997). Moreover, animal studies have shown that the intensity of maternal care depends on the "demand" of the offspring, which is in turn correlated with their corticosterone levels (Moles, Sarli, Bartolomucci, & D'Amato, 2008). These findings point to the fact that early maternal care can be triggered by the offspring, but can also contribute to differential programming of stress response systems and might thus be reflected in the behavioral and physiological profile of the young or adult offspring.

In human full-term children, quality of parental care as measured by maternal interactive behaviors is associated with children's cognitive as well as social abilities later in life (e.g., Landry, Smith, Miller-Loncar, & Swank, 1998). Importantly, the development of preterm children is influenced heavily by environment and contextual factors (e.g., Forcada-Guex, Pierrehumbert, Borghini, Moessinger, & Muller-Nix, 2006; Muller-Nix et al., 2004), and preterm children appear to be more sensitive to environmental perturbations than full-term children (e.g., Tu, Grunau, Petrie-Thomas, et al., 2007).

In infants and children born full-term, there is a sizable body of research indicating that cortisol levels are correlated with maternal care (e.g., Blair, Granger, Willoughby, & Kivlighan, 2006; Gunnar, 1998; Kerbel, Mertesacker, & Pauli-Pott, 2004; Thompson & Trevathan, 2008). In particular, mother-infant attachment and maternal sensitivity have been associated with infant stress reactivity (Blair et al., 2006; Spangler & Grossmann, 1993; Spangler, Schieche, Ilg, Maier, & Ackermann, 1994). However, increases in cortisol are not always associated with behavioral distress in the infant (Gunnar, 1989), which underlines the importance of measuring cortisol levels in addition to observing maternal and child behavior and interaction.

In preterm infants and children, little is known about relationships between cortisol and mother–child interactions. The style of interaction has been shown to differ between preterm and full-term mother–child dyads, potentially affecting their relationship and the developmental outcome of the offspring (Forcada-Guex et al., 2006). Previously, we found in the same cohort at 8 months CA, that maternal parenting stress and interactive behaviors mediated relationships between cortisol and attention (Tu, Grunau, Petrie-Thomas, et al., 2007). Alterations in the capacity of children born very preterm to regulate basal or stress cortisol levels may influence mother–child interaction, and may underlie the higher anxiety and depressive symptoms evident as early as the second year of life (Spittle et al., 2009; Vinall, Grunau, Miller, Synnes, & Whifield, 2010), as well as in adolescence (e.g., Grunau, Whitfield, & Fay, 2004; Levy-Shiff, Einat, Mogilner, Lerman, & Krikler, 1994). Early stress is associated with greater anxiety behaviors in adulthood in animal models (Kikusui & Mori, 2009; Lukkes, Watt, Lowry, & Forster, 2009), and patterns of cortisol secretion are altered in association with anxiety and depression in children born full-term (Essex, Klein, Slattery, Goldsmith, & Kalin, 2010). Therefore potentially complicated relationships between cortisol levels, mother interaction, and child behavior need more attention, especially in children born very preterm who show altered HPA axis functioning.

The aims of the present study at 18 months CA were to: (1) compare the patterns of cortisol responsiveness to a cognitive assessment in children born at varying degrees of prematurity (ELGA, VLGA) or full-term; (2) investigate relationships between maternal interactive behaviors and child cortisol levels; and (3) examine whether child cortisol levels are related to maternal ratings of child anxiety and depressive symptoms. We hypothesized that children born ELGA will show the most altered pattern of cortisol responses to the cognitive challenge, due to underlying differences in HPA regulation. Further, mother interactive behaviors may be differentially related to cortisol levels in ELGA, VLGA and full-term children and higher cortisol levels may be associated with anxiety/depressive behaviors, especially in the most vulnerable children, those born ELGA.

METHODS

Subjects

Participants, $N = 73$ mother-child pairs (25 born at extremely low gestational age [ELGA; 24–28 weeks], 26 very low gestational age [VLGA; 29–32 weeks] and 22 full-term [39–41 weeks]), were part of a larger longitudinal cohort participating in a study of long term effects of pain-related stress (e.g., Grunau, Weinberg, & Whitfield, 2004; Grunau et al., 2009; Haley, Weinberg, & Grunau, 2006; Tu, Grunau, Petrie-Thomas, et al., 2007). Children in the present study were selected from the larger cohort, to include only those born with birth weight appropriate for gestational age, and to exclude children with postnatal corticosteroid (dexamethasone) exposure, major congenital anomaly, major neurosensory impairment (blindness, cerebral palsy, sensorineural hearing impairment), severe brain injury evident on neonatal ultrasound (periventricular leukomalacia or grade 3 or 4 intraventricular hemorrhage), or maternal report of illicit hard drug use during pregnancy. In addition, only singleton births were included due to variations in maternal interaction in multiples compared to singletons among low birth weight children (Goldberg, Perrotta, Minde, & Corter, 1986; Rodder et al., 2004). We did not exclude children whose mothers received steroids antenatally ($n = 3$), or at delivery ($n = 40$), as this is standard procedure to enhance infant lung development prior to or during threatened preterm labor and would exclude most of the subjects.

The preterm children were recruited from the NICU at the Children's and Women's (C&W) Health Centre of British Columbia. The full-term children were born at the same Centre and contacted through their pediatricians.

All procedures were approved by the University of British Columbia Clinical Research Ethics Board and the Children's and Women's Health Centre of British Columbia Research Review Committee, and written informed consent was obtained from the mother.

Measures

Child and Maternal Characteristics—Medical and nursing chart review was conducted by one neonatal research nurse to obtain neonatal information including but not limited to birth weight, gestational age, and illness severity of the infant (Score for Neonatal Acute Physiology, SNAPII; Richardson, Corcoran, Escobar, & Lee, 2001). Maternal demographic characteristics (maternal age, education level) were collected by questionnaire. Infant neonatal and maternal demographic characteristics are shown in Table 1.

Child Cortisol—To collect saliva, a small cotton dental roll was placed into the child's mouth for about 1 min and the saliva was later extracted through a syringe tube into a vial. Saliva samples were assayed using the Salimetrics High Sensitivity Salivary Cortisol Enzyme Immunoassay Kit for quantitative determination of salivary cortisol (Salimetrics LLC, State College, PA). All samples were run in duplicate. The intra- and inter-assay coefficients of variation were 3.04% and 6.57% respectively. Outliers (defined as a value >3 SD above the mean) were winsorized following the method of Tukey (1997) and retained for data analysis. Cortisol values were log transformed for statistical analyses after winsorizing. To control for circadian rhythm in cortisol levels, all visits were in the morning between 9 am and noon, and no children in the study were fed within 30 min of cortisol collection to avoid contamination of saliva samples that might affect cortisol assays.

Developmental Assessment—The Bayley Scales of Infant Development 2nd Edition (Bayley, 1993), the most widely used standardized tests of infant and toddler development, were administered. The Mental Development Index (MDI) measures cognitive and language function and includes eye-hand items such as stacking blocks, as well as concrete problem solving tasks, and receptive and expressive vocabulary items. The MDI has a mean of 100 and SD of 15.

Mother and Child Interactive Behaviors—Interactive parent and child behaviors during developmentally appropriate semi-structured teaching play was measured using a method validated on preterm and full-term infants and toddlers (Crnic, Ragozin, Greenberg, Robinson, & Basham, 1983; Grunau, 2003). The parent was asked to play as they would at home. The 5 min teaching task at 18 months CA involved an easier familiar task (stacking or nesting colored cups varying in size), and a novel difficult task (sorting plastic pigs and cows into containers). Mother and child behavior was videotaped and scored separately using two unobtrusive wall-mounted cameras. Mother behavior was rated on each of 4 measures on a scale from 1 (low) to 5 (high): Affect (from angry, irritated to happy, positive), Gratification (degree of enjoyment), Sensitivity (to infants cues; intrusiveness to synchrony), and Organization (difficult to follow themes, no focus, to well organized, and focused on each activity). The child was independently rated on Affect (from very angry/ negative to very happy/smiling), Gratification (from avoidance/no gratification to long periods of enjoyment, happiness), and Responsivity (from out of synchrony, intrusiveness/ avoidance to no intrusions, reciprocity/attention) (Crnic, Greenberg, Robinson, & Ragozin, 1984; Crnic et al., 1983). Coding was carried out from videotapes by two trained experienced blinded raters, a primary coder and a reliability coder. Inter-rater reliability was carried out on 25% of the samples. Weighted kappa using agreement within one scale point was 0.95, 1.0, 0.79, and 0.94 for Affect, Gratification, Sensitivity, and Organization, respectively.

Child Internalizing Behavior—The Child Behavior Checklist for Ages 1½-5 years (CBCL; Achenbach & Ruffle, 2000) was completed by the child's mother. The CBCL is widely used method of identifying problem behavior in children. The responses to 100 questions are rated on a Likert scale: 0 = Not True, 1 = Somewhat or Sometimes True, 2 = Very True or Often True. For this study, only scales that are associated with stress were used, specifically, four syndrome scales (Emotional Reactivity, Anxious/Depressive Symptoms, Withdrawn, Attention Problems), and two Diagnostic and Statistical Manual of Mental Disorders (DSM) scales (Anxiety Problems, Attention Deficit Hyperactivity Problems).

Procedures

Testing was conducted at 18 months CA, at the Children's & Women's Health Centre of BC. Upon arrival at the centre, the mother and child were given time to become comfortable in the testing environment, then children were seated on the mother's lap, and the study session started.

A saliva sample was collected prior to the start of testing (Pretest) to measure undisturbed cortisol levels. Then the mental scale of the Bayley Scales of Infant Development 2nd Ed. (1993) was administered, followed by collection of another saliva sample (Post 1). Then, mother–child interaction was videotaped. The last cortisol sample was collected about 20 min after mother–child interaction (Post 2), at the end of the session. Assessments and video coding were carried out blinded to all the child and family information. Developmental and parenting characteristics are provided in Table 2.

Statistical Analysis

Demographic and child characteristics were analyzed using one-way ANOVA to examine differences among the groups (ELGA, VLGA, full-term). Child cortisol levels were examined using repeated measures ANOVA, with the cortisol phase (Pretest, Post 1, Post 2) as a within group factor, group (ELGA, VLGA, full-term) as a between subject factor, and child cognitive Bayley score (MDI) as a covariate. Principal components analysis (PCA) was performed on the maternal interactive behaviors and separately on the child interactive behaviors. Associations between child cortisol levels and maternal and child behavior were analyzed using Pearson correlations.

RESULTS

Dimension Reduction for Maternal and Child Interactive Behaviors

Principal components analysis (PCA) was performed with no rotation on the set of four maternal interactive behaviors, resulting in two eigenvalues >1 (2.18 accounting for 54.6% of the variance and 1.01 accounting for 25.2% of the variance respectively), reflecting two maternal vectors of behavior: Affect/Gratification and Sensitivity/Organization generated from the PCA regression scores. PCA on the child interactive behaviors produced one eigenvalue of 1.72, accounting for 57.3% of the variance, reflecting a single child behavior score generated from the PCA regression scores.

Child Characteristics

As expected, ELGA infants had significantly higher scores in all neonatal factors (e.g., illness severity SNAPII, $p < 0.001$; skin breaking procedures, $p < 0.001$; days of ventilation, $p < 0.001$) compared to VLGA infants (see Tab. 1). On the Bayley scale, there was a significant difference by Group (ELGA, VLGA, and full-term) in cognitive development as measured by the Mental Development Index (MDI) ($F(2,86) = 3.53$ $p = 0.034$). Newman

Keuls post-hoc tests showed that the VLGA group did not differ significantly from full-terms, whereas the ELGA group had significantly lower cognitive scores compared to both VLGA and full-term children.

Child interactive behavior during the Mother–Child interaction task was analyzed controlling for maternal Affect/Gratification and Sensitivity/Organization. There were no significant differences between the groups ($F(2,81) = 1.35$, $p = 0.26$) and no significant interaction with maternal behaviors. Maternal interactive behavior was also not significantly different between the groups (Affect/Gratification: $p = 0.89$; Sensitivity/Organization: $p = 0.41$) (see Tab. 2). In the current restricted sample, MANOVA on parent ratings of behavior on the CBCL (*T*-scores) showed no differences among the groups, unlike differences reported in the broader cohort (Vinall et al., 2010).

Salivary Cortisol Levels

All mother infant dyads were seen in the morning (mean, SD: 9:45 am ±40 min), with no significant difference between the groups for the time of the Pretest sample ($p = 0.13$) or the duration of the Bayley testing ($p = 0.80$).

Since the groups differed in cognitive function (MDI), which may differentially affect cortisol during cognitive challenge, MDI was entered as a covariate in evaluating differences in cortisol levels among the groups. Although there was no main effect of MDI ($F < 1$), there was a linear association between MDI and cortisol phase that approached significance ($p = 0.074$), and thus MDI was retained as a covariate. Repeated measures ANOVA (controlling for MDI) revealed a significant interaction between Testing phase and Group ($p = 0.005$), with a modest effect size $\eta = 0.10$. Between Group effects showed that under pretest conditions, ELGA children had significantly higher cortisol levels than VLGA ($p = 0.007$) and full-terms ($p = 0.019$). Within group comparison showed a significant drop in cortisol levels in the ELGA group between Pretest and the Post 1 time point ($p < 0.001$), with no further change to Post 2 ($p = 0.61$). In contrast, full-term children exhibited a significant drop between Pretest and Post 1 ($p = 0.016$), which was then followed by an increase in cortisol levels back to pretest levels at Post 2 ($p = 0.033$). The VLGA group also a small non-significant drop ($p = 0.15$), followed by a significant increase ($p = 0.037$) to pretest levels.

Cortisol values were significantly correlated at all three time points: Pretest with Post 1 ($r = 0.63$, $p < 0.001$) and Post 2 ($r = 0.39$, $p = 0.001$) and Post 1 with Post 2 ($r = 0.72$, $p < 0.001$). Figure 1 shows actual cortisol levels in all threes groups across the phases.

Child Cortisol and Maternal Interactive Behavior

First, we investigated whether there was an association between cortisol levels and child interactive behavior, as this might affect correlations between cortisol and maternal interaction. Partial correlations controlling for maternal behavior, revealed significant negative correlations between child interactive behavior and cortisol levels at the Post 1 and Post 2 time points in ELGA children only (Post 1 $r = -0.523$, $p = 0.012$; Post 2 $r = -0.43$, $p = 0.046$), indicating that higher cortisol levels during cognitive assessment (Post 1) and at the end of the session (Post 2), were associated with less optimal child interactive behavior assessed during the mother–child play task. Therefore, the subsequent correlations investigating maternal interaction and child cortisol levels were performed controlling for child behavior.

We found significant negative correlations between Pretest ($r = -0.47$, $p = 0.030$) and Post 1 ($r = -0.48$, $p = 0.027$) but not Post 2 ($r = -0.345$, $p = 0.12$) cortisol levels of ELGA children and mother Affect/Gratification (see Figs. 2 and 3), indicating that higher cortisol levels

during the Pretest and cognitive challenge phases were associated with poorer mother interactive behavior, independent of child behavior. In addition, mother's Sensitivity/Organization was negatively correlated with cortisol levels at Post 1 ($r = -0.49$, $p = 0.025$) and the Post 2 ($r = -0.43$ $p = 0.050$) but not at Pretest in ELGA children ($r = -0.33$, $p = 0.15$). In contrast, VLGA children's cortisol levels were significantly correlated only with mother's Affect/Gratification at the Post 1 time point ($r = -0.42$, $p = 0.036$), while cortisol levels of full-term children showed no correlations with maternal behavior. Further, there was no significant correlation between maternal behavior and Post 2 cortisol levels for any of the groups (all p's > 0.07). We also analyzed the association between maternal interaction behaviors and the change in cortisol levels between the sampling times (Pretest to Post 1 and Post 1 to Post 2), but found no significant correlations. Data are presented in Table 3.

Child Cortisol and Child Internalizing Behavior from CBCL Mother Ratings

There were significant correlations between selected CBCL behaviors and Pretest cortisol levels and the change from Pretest levels to Post 1, which are presented in Table 4. ELGA children showed strong correlations between Pretest or change in cortisol from Pretest to Post 1 levels and almost all selected CBCL behaviors, including Emotional Reactivity (Pretest: $r = 0.40$, change: $r = -0.45$), Anxious/Depressive Symptoms (Pretest: $r = 0.45$, change: $r = -0.46$), Withdrawn (Pretest: $r = 0.47$, change: $r = -0.53$), Attention Problems (Pretest: $r = 0.37$, change: $r = -0.49$) and Attention Deficit/Hyperactivity (ADH) Problems (Pretest: $r = 0.52$, change: $r = -0.45$). In all cases, children with higher internalizing behaviors showed higher Pretest cortisol levels and more prominent changes from Pretest to Post 1. VLGA children showed significant correlations between change in cortisol and Anxiety problems ($r = -0.73$) or Anxious/Depressive Symptoms ($r = -0.51$) and between Pretest cortisol and Anxiety Problems ($r = 0.55$). It is noteworthy that we found strong and statistically significant correlations despite our small sample size (Cohen, 1992). For the change in cortisol from Post 1 to Post 2, the only significant correlation was in the ELGA group, where lower cortisol change was associated with greater ADH problems ($r = -0.43$; $p = 0.048$) (data not shown). There were no significant correlations between any behavior and cortisol levels in full-term children (all $p > 0.45$).

DISCUSSION

There were three novel findings in the present study: first, at 18 months CA the pattern of cortisol response to cognitive challenge was different in children born ELGA compared to VLGA and full-term; second, maternal interaction (controlling for child behavior) influenced cortisol levels in the ELGA children, but very little in the VLGA and not in full-terms; and third, pretest cortisol levels and the pattern of change across the phases was associated with stress-sensitive internalizing behaviors in the preterm but not the full-term children.

In our carefully selected sample, in which children exposed to the stress of multiple gestation and/or fetal growth restriction were excluded, ELGA children displayed higher pretest cortisol levels than VLGA and full-terms at 18 months CA, consistent with our previous results in a larger more heterogeneous cohort (Grunau et al., 2007). All three groups of children showed an initial drop in cortisol from pretest to the end of cognitive testing, but the decrease was greatest in the ELGA group (given higher pretest values). Importantly, cortisol levels of the ELGA children remained low to the end of the session, whereas VLGA and full-term children exhibited an increase or recovery of cortisol back to pretest levels at the end of the session.

The cortisol response pattern for the VLGA and full-term children (initial slight drop followed by an increase back to pretest levels) was consistent with the pattern seen in VLGA

and full-term children from the same cohort at a younger age (8 months CA) in response to a visual attention task (Grunau, Weinberg, et al., 2004). Furthermore, consistent with previous literature on children born full-term (reviewed in Gunnar & Donzella, 2002), neither novel stimuli at 8 months CA (Grunau, Weinberg, et al., 2004) nor cognitive assessment in the present study, elicited an increase in cortisol in any group, demonstrating that in a number of different settings cortisol levels may be lowered below baseline or induce no change in cortisol levels (Gunnar, Talge, & Herrera, 2009; Jansen, Beijers, Riksen-Walraven, & de, 2010). Moreover, the literature suggests that the power to increase cortisol varies widely across psychological tasks and often requires uncontrollable social threat besides a cognitive challenge (Dickerson & Kemeny, 2004). Throughout the toddler and preschool years it is generally difficult to provoke an increase in cortisol in response to mildly threatening situations or to events that elicit distress, wariness and inhibition of approach, thus there may be a dissociation between the cortisol response and the expression of behavioral distress.

Of particular note, we only found significant differences in the pattern of cortisol levels in ELGA compared to full-term children but not between VLGA and full-term. This suggests that the length of gestation, and thereby maturation of physiological systems, is crucial to the developmental trajectory of the HPA axis following preterm birth, and that VLGA children appear better able to cope with the early life challenges of neonatal stressors. Therefore, it is essential to distinguish between these gestational age groups when comparing them to full-term children, as generalising may obscure some effects.

Our present findings and previously observed altered HPA responses during various situations at different stages of development (e.g., Grunau et al., 2005; Tu, Grunau, Petrie-Thomas, et al., 2007) suggests differential early programming of the HPA axis in ELGA compared to VLGA and term-born children, that appears to persist to school age (Buske-Kirschbaum et al., 2007). Early programming of the HPA axis has long been established in animal models (for review see Welberg & Seckl, 2001). Early adverse experiences such as gestational, maternal or separation stress not only result in altered stress hormone responses but also change the behavioral and cognitive outcome throughout the preweaning period and into adulthood (Brummelte, Pawluski, & Galea, 2006; Maccari & Morley-Fletcher, 2007; Matthews, 2002; Meaney et al., 2007). The seminal work of Meaney and colleagues demonstrated the role of postnatal maternal care in neurobiological outcomes by showing that maternal care in rats can reprogram HPA and behavioral responsiveness of the offspring via epigentic mechanisms (for review see Meaney et al., 2007). Preterm infants may be especially vulnerable to early postnatal programming of the neuroendocrine system, as they face many challenges during their first weeks of life ex utero. They are exposed to repeated procedures in the NICU (e.g., blood sampling, suctioning) as well as routines such as, weighing and clustered nursing care, which are stressful for very preterm neonates (Grunau et al., 2005, 2006; Holsti, Weinberg, Whitfield, & Grunau, 2007). Interestingly, a higher number of neonatal skin breaking procedures was shown to be associated with lower cortisol levels at 32 weeks gestational age while infants are exposed to ongoing stress, but higher cortisol levels later long after NICU discharge, at 8 months CA, suggesting that early pain-related stress may be linked with HPA axis programming (Grunau, Weinberg, et al., 2004, Grunau, Weinberg, et al., 2005, Grunau, Weinberg, et al., 2007).

Approaches to minimize or prevent the consequences of early stress and alterations in endogenous glucocorticoid exposure may have important therapeutic impact (Welberg & Seckl, 2001). It has long been known that positive mother–child interaction and maternal sensitivity is correlated with a better cognitive and behavioral outcome of the (full-term) offspring (Beckwith, Rodning, & Cohen, 1992; Bergman, Sarkar, Glover, & O'Connor, 2008; Donovan & Leavitt, 1978). Preterm children are especially sensitive to positive and

supportive maternal care. For example, lower parenting stress has been shown to buffer effects of cumulative neonatal pain on cognition in 18-month-old preterm children (Grunau et al., 2009) and greater interactive maternal behavior of parents reporting lower parenting stress was associated with better focused attention in 8-month-old preterm infants (Tu, Grunau, Petrie-Thomas, et al., 2007). While mothers of preterm children have been reported to be more controlling and less sensitive and responsive, which predicts differences in interactive behavior and less favourable child outcome (Forcada-Guex et al., 2006; Muller-Nix et al., 2004; Smith, Landry, & Swank, 2006), the direction of effects is unknown since child developmental delays and dysregulated behavior is rarely accounted for. Importantly, in the present study, we controlled for child behavior when evaluating mother behavior.

Until the present study, very little was known about relationships between mother–child interactions and cortisol pattern in preterm children. We found that ELGA children whose mothers displayed lower Affect/Gratification had higher pretest and cognitive assessment cortisol levels, whereas greater maternal Sensitivity/Organization was associated with lower cortisol levels among ELGA children during cognitive assessment and at the end of the session. In contrast, full-term children revealed no association between maternal interactive behaviors and child cortisol levels at 18 months of age, consistent with other studies showing that preterm children or children at risk are more responsive to maternal care and mood than full-term children (e.g., Bugental, Beaulieu, & Schwartz, 2008; Kaplan, Evans, & Monk, 2008; Thompson & Trevathan, 2008; Tu, Grunau, Petrie-Thomas, et al., 2007). Taken together, our results show that more positive maternal behavior is associated with lower cortisol levels in preterm children, independent of child behavior. Therfore, it is conceivable that the influence of maternal care on the outcome of the preterm child is, at least partly, mediated through different activation of the HPA axis.

Importantly, those ELGA children who were able to modulate (decrease) their cortisol levels from the higher pretest levels to lower levels during cognitive challenge, had lower mother ratings of child emotional reactivity, anxiety, depressive symptoms, withdrawal, attention, and attention disorder/hyperactivity (ADH) behaviors. These correlations were all in the moderate to high range of effect size (Cohen, 1992). Interestingly, among the VLGA children, higher pretest cortisol and reduced capacity to return to basal levels were specifically associated with higher ratings of anxiety problems and anxious/depressive symptoms, but not emotional reactivity or attention problems. Internalizing symptoms have recently been reported in very preterm children as young as 1½-2 years of age (Spittle et al., 2009; Vinall et al., 2010), and increased prevalence of anxiety/depressive symptoms or internalizing behavior problems is seen in preterm adolescents and young adults (e.g. Grunau, Whitfield, et al., 2004; Levy-Shiff et al., 1994; Schmidt, Miskovic, Boyle, & Saigal, 2010). Our findings that more symptoms of internalizing behavior were associated with higher cortisol levels in ELGA and to a lesser degree VLGA children at 18 months CA is consistent with studies showing that cortisol levels are associated with higher internalizing symptoms in 2-year-old full-term children (de Haan, Gunnar, Tout, Hart, & Stansbury, 1998). In line with this, insecure and inhibited full-term children at age 18 months show a greater cortisol increase in response to a strange situation and challenging coping episode compared to uninhibited children, regardless of their maternal attachment (Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996). Furthermore, securely attached infants show decreased stress-induced HPA axis activation compared to insecurely attached and disorganized infants, and thus better coping with a stressful situation (Spangler & Grossmann, 1993). Moreover, adrenocortical reactivity to social challenge is associated with more internalizing problems in clinic-referred children and adolescents (Granger, Weisz, McCracken, Ikeda, & Douglas, 1996) and higher cortisol levels in low birth weight adults are related to greater relative right frontal electroencephalogram activity, which in turn is related to more internalizing behavior problems (Schmidt et al., 2010). Therefore differences

in child capacity to regulate basal or stress cortisol levels, may contribute to the higher anxiety and depressive symptoms evident later in children born very preterm (Grunau, Whitfield, et al., 2004; Levy-Shiff et al., 1994; Spittle et al., 2009; Tu, Grunau, Weinberg, & Whitfield, 2007). To our knowledge this is the first study to examine internalizing in relation to cortisol in preterm children, and suggests that more research into dysregulated cortisol activity is important for understanding these behaviors in preterm children.

Children born preterm frequently show poorer long-term outcome in cognitive and behavioral development persisting to adolescence or adulthood (e.g., Grunau, Whitfield, et al., 2004; Hack, 2009; Marlow, 2004). It has been suggested that altered stress-sensitive outcomes in preterm children may at least in part be due to alterations in the development of the HPA system (Grunau et al., 2006). Considering the higher baseline cortisol levels in 18 month old preterm children seen in the present study, in our larger heterogeneous cohort (Grunau et al., 2007), and in wakening levels in adolescents born preterm (Buske-Kirschbaum et al., 2007), it is conceivable that early dysregulation in the HPA axis may have long lasting and potentially permanent effects on the neurodevelopment and behavior of ELGA children. This is in line with the adverse effects of high glucocorticoid levels on cognitive function and anxiety behaviors in animals and humans (Brummelte et al., 2006; Ferris & Stolberg, 2010; Lupien et al., 1999; Seckl & Holmes, 2007).

CONCLUSIONS

Important strengths of the present study included the carefully defined subject selection of preterm children to reduce the potentially confounding effects of other factors that might affect the HPA axis (e.g., in utero growth retardation, multiple gestation, and postnatal glucocorticoid treatment), and the examination of associations of cortisol levels with maternal behavior controlling for child behavior. A limitation of this study was that the sample size did not permit comparisons of male and female children. Our findings of altered pattern of cortisol responses to cognitive stress, and associations between cortisol levels and stress-related anxiety and withdrawal behaviors at 18 months CA in ELGA children, are consistent with the concept of altered early programming of HPA axis function in children born extremely preterm, compared to that in more mature preterm and full-term children. Furthermore, the novel finding that cortisol levels were correlated with maternal behavior in preterm but not full-term children suggests that HPA function may be differentially regulated in ELGA compared to VLGA and term born children at 18 months CA, and that their neuroendocrine development might be more sensitive to the environmental context of child rearing. This underlines the importance of investigating the role of sensitive and responsive caregiving, as well as mother organization, in buffering reactivity of the HPA system in preterm children. Support for this comes from our finding that the pattern of cortisol levels was related to anxiety and withdrawal symptoms in preterm but not the full-term children. Given the importance of glucocorticoid regulation for cognitive function alterations in the HPA axis in children born extremely preterm may contribute to their altered cognition and behavior. Understanding the etiology and processes involved in HPA regulation in this vulnerable population is important for improving long-term outcomes.

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References

Achenbach TM, Ruffle TM. The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. Pediatrics in Review. 2000; 21:265–271. [PubMed: 10922023]

Bayley, N. Bayley scales of infant development. 2nd ed.. San Antonio: TX-Psychological Corporation; 1993.

Beckwith L, Rodning C, Cohen S. Preterm children at early adolescence and continuity and discontinuity in maternal responsiveness from infancy. Child Development. 1992; 63:1198–1208. [PubMed: 1446549]

Bergman K, Sarkar P, Glover V, O'Connor TG. Quality of child-parent attachment moderates the impact of antenatal stress on child fearfulness. Journal of Child Psychology and Psychiatry. 2008; 49:1089–1098. [PubMed: 19017025]

Blair C, Granger D, Willoughby M, Kivlighan K. Maternal sensitivity is related to hypothalamic-pituitary-adrenal axis stress reactivity and regulation in response to emotion challenge in 6-month-old infants. Annals of the New York Academy of Sciences. 2006; 1094:263–267. [PubMed: 17347358]

Brummelte S, Pawluski JL, Galea LA. High post-partum levels of corticosterone given to dams influence postnatal hippocampal cell proliferation and behavior of offspring: A model of post-partum stress and possible depression. Hormones and Behavior. 2006; 50:370–382. [PubMed: 16780843]

Bugental DB, Beaulieu D, Schwartz A. Hormonal sensitivity of preterm versus full-term infants to the effects of maternal depression. Infant Behavior and Development. 2008; 31:51–61. [PubMed: 17645947]

Buske-Kirschbaum A, Krieger S, Wilkes C, Rauh W, Weiss S, Hellhammer DH. Hypothalamic-pituitary-adrenal axis function and the cellular immune response in former preterm children. Journal of Clinical Endocrinology and Metabolism. 2007; 92:3429–3435. [PubMed: 17566098]

Champagne FA, Curley JP. Epigenetic mechanisms mediating the long-term effects of maternal care on development. Neuroscience and Biobehavioral Reviews. 2009; 33:593–600. [PubMed: 18430469]

Champagne F, Meaney MJ. Like mother, like daughter: Evidence for non-genomic transmission of parental behavior and stress responsivity. Progress in Brain Research. 2001; 133:287–302. [PubMed: 11589138]

Cohen J. A power primer. Psychological Bulletin. 1992; 112:155–159. [PubMed: 19565683]

Crnic KA, Greenberg MT, Robinson NM, Ragozin AS. Maternal stress and social support: Effects on the mother-infant relationship from birth to eighteen months. American Journal of Orthopsychiatry. 1984; 54:224–235. [PubMed: 6731590]

Crnic KA, Ragozin AS, Greenberg MT, Robinson NM, Basham RB. Social interaction and developmental competence of preterm and full-term infants during the first year of life. Child Development. 1983; 54:1199–1210. [PubMed: 6354627]

de Haan M, Gunnar MR, Tout K, Hart J, Stansbury K. Familiar and novel contexts yield different associations between cortisol and behavior among 2-year-old children. Developmental Psychobiology. 1998; 33:93–101. [PubMed: 9664174]

Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. Psychological Bulletin. 2004; 130:355–391. [PubMed: 15122924]

Donovan WL, Leavitt LA. Early cognitive development and its relation to maternal physiologic and behavioral responsiveness. Child Development. 1978; 49:1251–1254. [PubMed: 738158]

Essex MJ, Klein MH, Slattery MJ, Goldsmith HH, Kalin NH. Early risk factors and developmental pathways to chronic high inhibition and social anxiety disorder in adolescence. American Journal of Psychiatry. 2010; 167:40–46. [PubMed: 19917594]

Fernandez EF, Montman R, Watterberg KL. ACTH and cortisol response to critical illness in term and late preterm newborns. Journal of Perinatology. 2008; 28:797–802. [PubMed: 18987643]

Ferris CF, Stolberg T. Imaging the immediate non-genomic effects of stress hormone on brain activity. Psychoneuroendocrinology. 2010; 35:5–14. [PubMed: 19783105]

Forcada-Guex M, Pierrehumbert B, Borghini A, Moessinger A, Muller-Nix C. Early dyadic patterns of mother-infant interactions and outcomes of prematurity at 18 months. Pediatrics. 2006; 118:e107–e114. [PubMed: 16818525]

Goldberg S, Perrotta M, Minde K, Corter C. Maternal behavior and attachment in low-birth-weight twins and singletons. Child Development. 1986; 57:34–46. [PubMed: 3948593]

Granger DA, Weisz JR, McCracken JT, Ikeda SC, Douglas P. Reciprocal influences among adrenocortical activation, psychosocial processes, and the behavioral adjustment of clinic-referred children. Child Development. 1996; 67:3250–3262. [PubMed: 9071780]

Grunau, RE. Self-regulation and behavior in preterm children: Effects of early pain. In: McGrath, PJ.; Finley, GA., editors. Pediatric pain: Biological and social context, progress in pain research and management. Seattle: IASP Press; 2003. p. 23-55.

Grunau RE, Haley DW, Whitfield MF, Weinberg J, Yu W, Thiessen P. Altered basal cortisol levels at 3, 6, 8 and 18 months in infants born at extremely low gestational age. Journal of Pediatrics. 2007; 150:151–156. [PubMed: 17236892]

Grunau RE, Holsti L, Haley DW, Oberlander T, Weinberg J, Solimano A, Whitfield MF, Fitzgerald C, Yu W. Neonatal procedural pain exposure predicts lower cortisol and behavioral reactivity in preterm infants in the NICU. Pain. 2005; 113:293–300. [PubMed: 15661436]

Grunau RE, Holsti L, Peters JW. Long-term consequences of pain in human neonates. Seminars in Fetal and Neonatal Medicine. 2006; 11:268–275. [PubMed: 16632415]

Grunau RE, Weinberg J, Whitfield MF. Neonatal procedural pain and preterm infant cortisol response to novelty at 8 months. Pediatrics. 2004; 114:e77–e84. [PubMed: 15231977]

Grunau RE, Whitfield MF, Fay TB. Psychosocial and academic characteristics of extremely low birth weight (≤800 g) adolescents who are free of major impairment compared with term-born control subjects. Pediatrics. 2004; 114:e725–e732. [PubMed: 15576337]

Grunau RE, Whitfield MF, Petrie-Thomas J, Synnes AR, Cepeda IL, Keidar A, Rogers M, Mackay M, Hubber-Richard P, Johannesen D. Neonatal pain, parenting stress and interaction, in relation to cognitive and motor development at 8 and 18 months in preterm infants. Pain. 2009; 143:138–146. [PubMed: 19307058]

Gunnar MR. Studies of the human infant's adrenocortical response to potentially stressful events. New Directions for Child Development. 1989; 45:3–18. [PubMed: 2687726]

Gunnar MR. Quality of early care and buffering of neuroendocrine stress reactions: Potential effects on the developing human brain. Preventive Medicine. 1998; 27:208–211. [PubMed: 9578997]

Gunnar MR, Donzella B. Social regulation of the cortisol levels in early human development. Psychoneuroendocrinology. 2002; 27:199–220. [PubMed: 11750779]

Gunnar MR, Talge NM, Herrera A. Stressor paradigms in developmental studies: What does and does not work to produce mean increases in salivary cortisol. Psychoneuroendocrinology. 2009; 34:953–967. [PubMed: 19321267]

Hack M. Adult outcomes of preterm children. Journal of Developmental and Behavioral Pediatrics. 2009; 30:460–470. [PubMed: 19823140]

Haley DW, Weinberg J, Grunau RE. Cortisol, contingency learning, and memory in preterm and full-term infants. Psychoneuroendocrinology. 2006; 31:108–117. [PubMed: 16122876]

Hanna CE, Keith LD, Colasurdo MA, Buffkin DC, Laird MR, Mandel SH, Cook DM, LaFranchi SH, Reynolds JW. Hypothalamic pituitary adrenal function in the extremely low birth weight infant. Journal of Clinical Endocrinology and Metabolism. 1993; 76:384–387. [PubMed: 8381799]

Heim C, Nemeroff CB. Neurobiology of early life stress: Clinical studies. Seminars in Clinical Neuropsychiatry. 2002; 7:147–159. [PubMed: 11953939]

Herlenius E, Lagercrantz H. Development of neurotransmitter systems during critical periods. Experimental Neurology. 2004; 190 (Suppl 1):S8–S21. [PubMed: 15498537]

Holsti L, Weinberg J, Whitfield MF, Grunau RE. Relationships between adrenocorticotropic hormone and cortisol are altered during clustered nursing care in preterm infants born at extremely low gestational age. Early Human Development. 2007; 83:341–348. [PubMed: 16979857]

Jansen J, Beijers R, Riksen-Walraven M, de Weerth C. Cortisol reactivity in young infants. Psychoneuroendocrinology. 2010; 35:329–338. [PubMed: 19651476]

Kaplan LA, Evans L, Monk C. Effects of mothers' prenatal psychiatric status and postnatal caregiving on infant biobehavioral regulation: Can prenatal programming be modified? Early Human Development. 2008; 84:249–256. [PubMed: 17761394]

Kari MA, Raivio KO, Stenman UH, Voutilainen R. Serum cortisol, dehydroepiandrosterone sulfate, and steroid-binding globulins in preterm neonates: Effect of gestational age and dexamethasone therapy. Pediatric Research. 1996; 40:319–324. [PubMed: 8827784]

Kerbel B, Mertesacker B, Pauli-Pott U. Mother-infant interaction and adrenocortical reactivity in infancy. Psychotherapie, Psychosomatik, Medizinische Psychologie. 2004; 54:243–249.

Kikusui T, Mori Y. Behavioural and neurochemical consequences of early weaning in rodents. Journal of Neuroendocrinology. 2009; 21:427–431. [PubMed: 19207810]

Landry SH, Smith KE, Miller-Loncar CL, Swank PR. The relation of change in maternal interactive styles to the developing social competence of full-term and preterm children. Child Development. 1998; 69:105–123. [PubMed: 9499561]

Levy-Shiff R, Einat G, Mogilner MB, Lerman M, Krikler R. Biological and environmental correlates of developmental outcome of prematurely born infants in early adolescence. Journal of Pediatric Psychology. 1994; 19:63–78. [PubMed: 8151496]

Liu D, Diorio J, Tannenbaum B, Caldji C, Francis D, Freedman A, Sharma S, Pearson D, Plotsky PM, Meaney MJ. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. Science. 1997; 277:1659–1662. [PubMed: 9287218]

Lukkes JL, Watt MJ, Lowry CA, Forster GL. Consequences of post-weaning social isolation on anxiety behavior and related neural circuits in rodents. Frontiers in Behavioral Neuroscience. 2009; 3:18. [PubMed: 19738931]

Lupien SJ, Nair NP, Briere S, Maheu F, Tu MT, Lemay M, McEwen BS, Meaney MJ. Increased cortisol levels and impaired cognition in human aging: Implication for depression and dementia in later life. Reviews in the Neurosciences. 1999; 10:117–139. [PubMed: 10658955]

Maccari S, Morley-Fletcher S. Effects of prenatal restraint stress on the hypothalamus-pituitary-adrenal axis and related behavioural and neurobiological alterations. Psychoneuroendocrinology. 2007; 32 (Suppl 1):S10–S15. [PubMed: 17651905]

Marlow N. Neurocognitive outcome after very preterm birth. Archives of Disease in Childhood. Fetal and Neonatal Edition. 2004; 89:F224–F228. [PubMed: 15102725]

Matthews SG. Early programming of the hypothal-amo-pituitary-adrenal axis. Trends in Endocrinology & Metabolism. 2002; 13:373–380. [PubMed: 12367818]

Meaney MJ, Szyf M, Seckl JR. Epigenetic mechanisms of perinatal programming of hypothalamic-pituitary-adrenal function and health. Trends in Molecular Medicine. 2007; 13:269–277. [PubMed: 17544850]

Miller SP, Mayer EE, Clyman RI, Glidden DV, Hamrick SE, Barkovich AJ. Prolonged indomethacin exposure is associated with decreased white matter injury detected with magnetic resonance imaging in premature newborns at 24 to 28 weeks' gestation at birth. Pediatrics. 2006; 117:1626–1631. [PubMed: 16651316]

Moles A, Sarli C, Bartolomucci A, D'Amato FR. Interaction with stressed mothers affects corticosterone levels in pups after reunion and impairs the response to dexamethasone in adult mice. Psychoneuroendocrinology. 2008; 33:462–470. [PubMed: 18308478]

Muller-Nix C, Forcada-Guex M, Pierrehumbert B, Jaunin L, Borghini A, Ansermet F. Prematurity, maternal stress and mother–child interactions. Early Human Development. 2004; 79:145–158. [PubMed: 15324994]

Nachmias M, Gunnar M, Mangelsdorf S, Parritz RH, Buss K. Behavioral inhibition and stress reactivity: The moderating role of attachment security. Child Development. 1996; 67:508–522. [PubMed: 8625725]

Retz W, Kornhuber J, Riederer P. Neuro-transmission and the ontogeny of human brain. Journal of Neural Transmission. 1996; 103:403–419. [PubMed: 9617785]

Richardson DK, Corcoran JD, Escobar GJ, Lee SK. SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores. Journal of Pediatrics. 2001; 138:92–100. [PubMed: 11148519]

Rodder D, Ganseforth C, Pillekamp F, Kribs A, von GA, Roth B, Schleiffer R. Mother–infant interactions with very low birth weight multiple newborns (<1500 g). A comparison of mother-multiple and mother-single births. Zeitschrift fur Geburtshilfe und Neonatologie. 2004; 208:174–183. [PubMed: 15508051]

Schmidt LA, Miskovic V, Boyle M, Saigal S. Frontal electroencephalogram asymmetry, salivary cortisol, and internalizing behavior problems in young adults who were born at extremely low birth weight. Child Development. 2010; 81:183–199. [PubMed: 20331661]

Seckl JR, Holmes MC. Mechanisms of disease: Glucocorticoids, their placental metabolism and fetal 'programming' of adult pathophysiology. Nature Clinical Practice Endocrinology & Metabolism. 2007; 3:479–488.

Smith KE, Landry SH, Swank PR. The role of early maternal responsiveness in supporting school-aged cognitive development for children who vary in birth status. Pediatrics. 2006; 117:1608–1617. [PubMed: 16651314]

Spangler G, Grossmann KE. Biobehavioral organization in securely and insecurely attached infants. Child Development. 1993; 64:1439–1450. [PubMed: 8222882]

Spangler G, Schieche M, Ilg U, Maier U, Ackermann C. Maternal sensitivity as an external organizer for biobehavioral regulation in infancy. Developmental Psychobiology. 1994; 27:425–437. [PubMed: 7843497]

Spittle AJ, Treyvaud K, Doyle LW, Roberts G, Lee KJ, Inder TE, Cheong JL, Hunt RW, Newnham CA, Anderson PJ. Early emergence of behavior and social-emotional problems in very preterm infants. Journal of the American Academy of Child and Adolescent Psychiatry. 2009; 48:909–918. [PubMed: 19633579]

Thompson LA, Trevathan WR. Cortisol reactivity, maternal sensitivity, and learning in 3-month-old infants. Infant Behavior and Development. 2008; 31:92–106. [PubMed: 17716739]

Tu MT, Grunau RE, Petrie-Thomas J, Haley DW, Weinberg J, Whitfield MF. Maternal stress and behavior modulate relationships between neonatal stress, attention, and basal cortisol at 8 months in preterm infants. Developmental Psychobiology. 2007; 49:150–164. [PubMed: 17299787]

Tu, MT.; Grunau, RE.; Weinberg, J.; Whitfield, MF. The interplay between infant basal cortisol, maternal parenting stress and internalizing behavior in extremely preterm and full-term infants at 18 months. Poster. Pediatric Academic Societies' Annual Meeting; Toronto. 2007. E-PAS2007: 616280.29

Tukey, JW. Exploratory data analysis. Don Mills, Ontario: Addison-Wesley; 1997.

Vinall, J.; Grunau, RE.; Miller, SP.; Synnes, AR.; Whifield, MF. Maternal emotional availability predicts lower internalizing behaviors for preterm and term born children at 18 months corrected age. Pediatric Academic Societies' Annual Meeting; 2010. p. 3731.317

Volpe JJ. Perinatal brain injury: From pathogenesis to neuroprotection. Mental Retardation and Developmental Disabilities Research Reviews. 2001; 7:56–64. [PubMed: 11241883]

Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ. Epigenetic programming by maternal behavior. Nature Neuroscience. 2004; 7:847–854.

Welberg LA, Seckl JR. Prenatal stress, glucocorticoids and the programming of the brain. Journal of Neuroendocrinology. 2001; 13:113–128. [PubMed: 11168837]

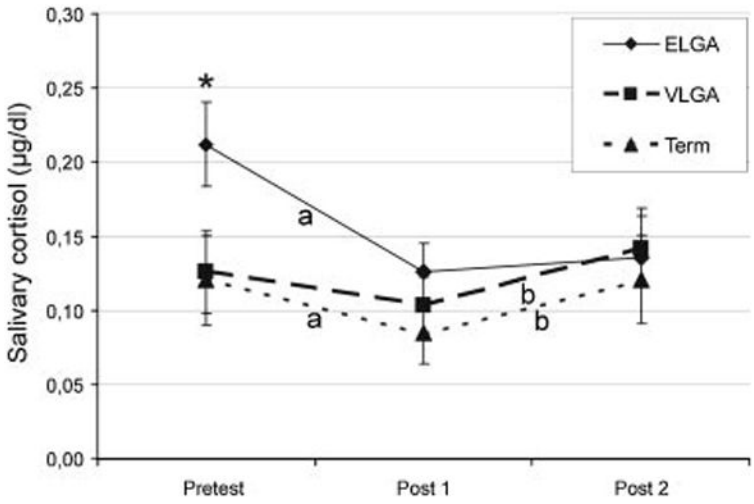

FIGURE 1.

Salivary cortisol at each phase (Pretest, Post 1 [following cognitive assessment], Post 2 [end of session]), for children born at extremely low gestational age (ELGA), very low gestational age (VLGA) and full-term at 18 months corrected age. *Indicates that ELGA children had significantly higher cortisol levels than VLGA ($p = 0.007$) and full-terms ($p = 0.019$); a and b indicate significant differences within groups between testing phases, with ELGA ($p < 0.001$) and full-term children ($p = 0.016$) showing a drop in cortisol levels between pretest and the Post 1 time and VLGA ($p = 0.037$) and full-term ($p = 0.033$) showing an increase in cortisol levels between Post 1 and Post 2.

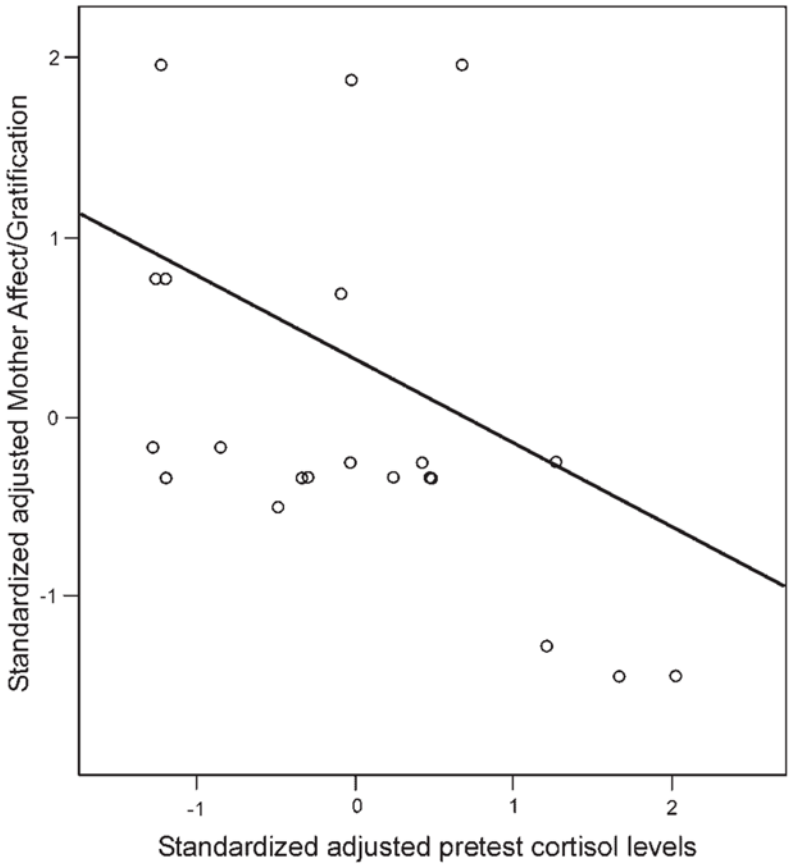

FIGURE 2.
Scatter plot of the relationship between pretest cortisol (winsorized and log transformed) and mother Affect/Gratification adjusted for infant interactive behavior in infants born extremely low gestational age (ELGA) at 18 months corrected age.

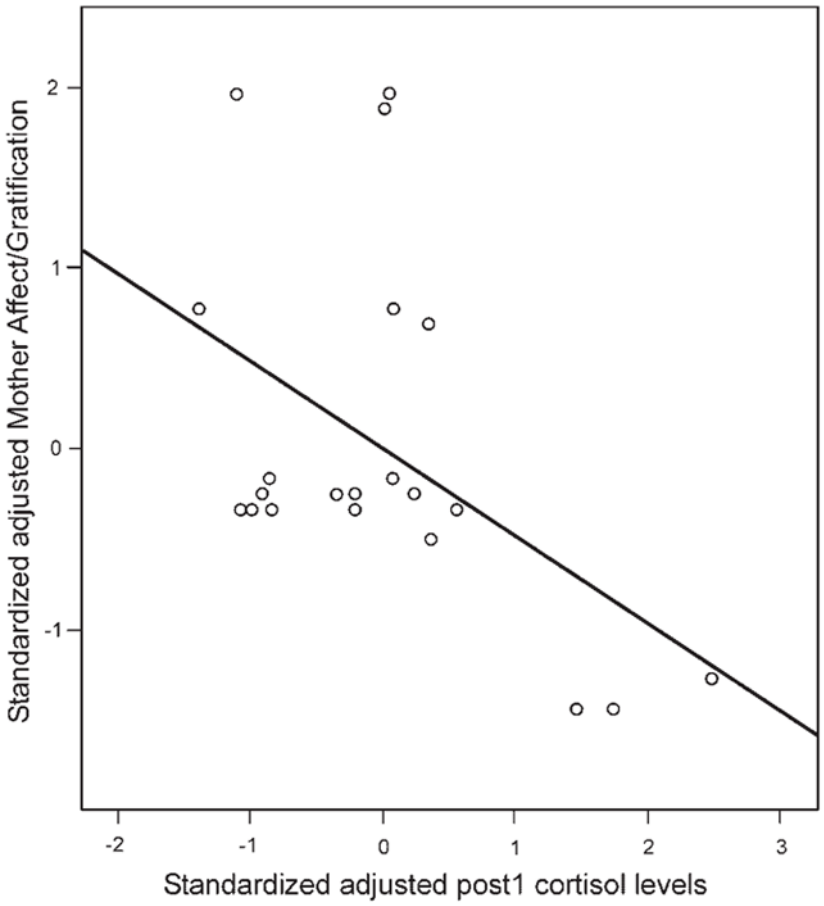

FIGURE 3.
Scatter plot of the relationship between cortisol levels (winsorized and log transformed) following cognitive assessment (Post 1) and mother Affect/Gratification adjusted for infant interactive behavior in infants born extremely low gestational age (ELGA) at 18 months corrected age.

Table 1

Child and Mother Characteristics

	ELGA (*n* = 25)	VLGA (*n* = 26)	Full-Term (*n* = 22)	*p*-Value
Gestational age at birth (weeks)	26.1 (1.4)[a,b]	31.2 (1.2)[b]	40.0 (1.1)	0.0001
Birth weight (g)	866.26 (204.03)[a,b]	1540.67 (338.04)[b]	3442.66 (311.90)	0.0001
Illness severity Day 1 (SNAP-II)	19.1 (12.5)[a]	3.3 (5.0)	—	0.001
Pain-related stress (number of skin-breaking procedures from birth to term)	203.4 (98.3)[a]	49.5 (21.8)	—	0.001
Mechanical ventilation (days)	30.6 (26.7)[a]	0.9 (1.9)	—	0.001
Sex (% male)	68%	58%	39%	0.13
Mother years of education (years)	14.1 (2.7)[b]	15.4 (3.3)	16.95 (3.38)	0.012
Mother age (years)	31.5 (6.2)	32.9 (5.2)	33.9 (5.4)	0.33

Infant characteristics differed for children born at extremely low gestational age (ELGA), very low gestational age (VLGA) and full-term. Unless otherwise indicated, values are mean and (SD): significantly different from

[a] VLGA and

[b] full-term infants.

Table 2

Developmental, Parenting, and Behavioral Characteristics at 18 Months (Mean and SD)

	ELGA (*n* = 25)	VLGA (*n* = 26)	Full-Term (*n* = 22)	*p*-Value
Bayley mental index (MDI)	84.9 (16.4)[a,b]	94.0 (16.4)	96.8 (11.3)	0.02[a], 0.05[b]
Mother interaction: affect/gratification	3.1 (0.4)	3.1 (0.5)	3.1 (0.5)	0.89
Mother interaction: sensitivity/organization	3.8 (0.6)	3.8 (0.5)	4.0 (0.7)	0.41
Child interaction	2.9 (0.3)	2.7 (0.6)	2.9 (0.4)	0.26
CBCL				
Emotional reactivity	52.3 (4.7)	53.3 (8.7)	51.8 (3.3)	0.69
Anxious/depressive symptoms	51.6 (4.1)	51.4 (3.2)	50.5 (0.7)	0.46
Withdrawn	53.0 (4.8)	51.9 (3.6)	51.6 (3.9)	0.51
Attention problems	54.9 (6.5)	52.9 (4.5)	51.9 (2.9)	0.12
Anxiety problems	51.6 (3.9)	51.5 (3.5)	51.1 (3.4)	0.90
Attention deficit hyperactivity (ADH) problems	52.7 (4.1)	52.5 (4.2)	51.7 (2.2)	0.61

There was no difference between extremely low gestational age (ELGA) or very low gestational age (VLGA) and full-term children in regards to mother or child interactive behavior or child internalizing behaviors rated by the mother on the Child Behavior Checklist (CBCL). However, ELGA children scored significantly lower on the Mental Development Index (MDI) compared to

[a] VLGA and

[b] full-term children.

Table 3

Correlations between Maternal Interaction Behavior (Controlling for Child Behavior) and Cortisol Pretest and Post 1

Maternal Interaction Behavior	ELGA	VLGA	Full-Term
Affect/gratification			
Pretest cortisol	−0.47*	0.20	−0.28
Post 1 cortisol	−0.48*	0.42*	0.04
Post 2 cortisol	−0.35	0.37	−0.06
Sensitivity/organization			
Pretest cortisol	−0.33	0.07	0.04
Post 1 cortisol	−0.49*	0.23	0.23
Post 2 cortisol	−0.43*	0.31	0.35

Maternal affect/gratification was negatively correlated with pretest and Post 1 cortisol levels in extremely low gestational age (ELGA) children and with Post 1 levels in very low gestational age (VLGA) children. Maternal Sensitivity/Organization was negatively correlated with Post 1 and Post 2 values in ELGA children. There were no associations between maternal behavior and cortisol levels in full-term children,

* $p < 0.05$.

Table 4

Correlations between CBCL Behavior Problems and Cortisol (Pretest, Change from Pretest to Cognitive Assessment [Post 1—Pretest])

Child Behavior Check List (CBCL) Problem	ELGA	VLGA	Full-Term
Emotional reactivity			
Pretest cortisol	0.40	0.11	−0.12
Change in cortisol (pretest to Post 1)	−0.45*	−0.25	−0.06
Anxious/depressive symptoms			
Pretest cortisol	0.45*	0.33	−0.15
Change in cortisol (pretest to Post 1)	−0.46*	−0.51*	−0.09
Withdrawn			
Pretest cortisol	0.47*	0.08	−0.08
Change in cortisol (pretest to Post 1)	−0.53*	−0.20	0.06
Attention problems			
Pretest cortisol	0.37	−0.17	0.08
Change in cortisol (pretest to Post 1)	−0.49*	0.05	0.01
Anxiety problems			
Pretest cortisol	0.34	0.55**	−0.17
Change in cortisol (pretest to Post 1)	−0.37	−0.73**	−0.01
Attention deficit hyperactivity (ADH) problems			
Pretest cortisol	0.52**	−0.19	−0.03
Change in cortisol (pretest to Post 1)	−0.61**	0.04	0.09

Extremely low gestational age (ELGA) children revealed the strongest relationships between cortisol and these behaviors, while very low gestational age (VLGA) children only showed significant correlations with anxious/depressive symptoms and anxiety problems. Full-term children showed no correlations with internalizing or attention behaviors.

* $p < 0.05$.

** $p < 0.01$.